

Amendments to the Claims

Please amend claims 1, 8, 12, 15, 16, and 24.

Please cancel claim 25.

The listing of claims will replace all prior versions, and listings of claims in the application.

Listing of Claims

1. (Currently Amended) A method for ~~the detection of the presence or absence of a~~
determining an increased likelihood of colorectal cell proliferative disorder or metastasis, cancer
in a human subject comprising:

~~determining, in a genomic DNA sample of a subject, a CpG methylation status of two~~
genes levels of ALX4 and TPEF and/or their regulatory sequences, in a biological sample
comprising colorectal cellular DNA obtained from the subject; and

~~comparing the methylation status with that of a normal colorectal DNA sample, wherein a~~
~~difference in the methylation status between the sample from the subject and the normal sample~~
level of ALX4 and TPEF in the sample with the methylation level in normal colorectal cellular
DNA, wherein a higher degree of methylation in the sample compared to the normal colorectal
cellular DNA is indicative of the presence or absence an increased likelihood of colorectal cell
proliferative disorder or metastasis cancer.

2. (Canceled)

3. (Canceled)

4. (Withdrawn) A method for the analysis of colorectal cell proliferative disorders,
comprising determining the CpG methylation status of the gene ALX4 and/or its regulatory
sequences, wherein based on said determined methylation status the presence or absence of a
colorectal cell proliferative disorder or metastasis is deduced.

5. (Canceled)

6. (Withdrawn) A nucleic acid molecule consisting essentially of a sequence at least 18 bases in length according to a sequences selected from the group consisting of SEQ ID NOS:7, 8, 15 and 16.

7. (Withdrawn) An oligomer, in particular an oligonucleotide or peptide nucleic acid (PNA)-oligomer, for the detection of colon cell proliferative disorders, said oligomer consisting essentially of at least one base sequence having a length of at least 20 contiguous nucleotides which is identical to a nucleic acid sequence selected from the group consisting of SEQ ID NOS:7, 8, 15 and 16 or to the complements thereof.

8. (Currently Amended) The method of claim 1, comprising:

contacting genomic DNA or a fragment thereof, obtained from a the subject, with one reagent or a plurality of reagents for distinguishing between methylated and non methylated CpG dinucleotide sequences within at least one target sequences of the genomic DNA or fragment thereof, wherein the target sequence comprises, or hybridizes under stringent conditions to, at least 16 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOS:7, 8, 9, 10, 15, 16, 17 and 18, ~~said~~ the contiguous nucleotides comprising at least one CpG dinucleotide sequence; and

determining, based at least in part on ~~said~~ the distinguishing, the methylation state of at least one target CpG dinucleotide sequence, or an average, or a value reflecting an average methylation state of a plurality of target CpG dinucleotide sequences, whereby detecting, or detecting colon cell proliferative disorders or metastasis is afforded.

9. (Original) The method of claim 8, wherein distinguishing between methylated and non methylated CpG dinucleotide sequences within the target sequence comprises converting unmethylated cytosine bases within the target sequence to uracil or to another base that is

detectably dissimilar to cytosine in terms of hybridization properties.

10. (Original) The method of claim 8, wherein the biological sample is selected from the group consisting of cell lines, histological slides, biopsies, paraffin-embedded tissue, bodily fluids, stool, blood, and combinations thereof.

11. (Previously Presented) The method of claim 8, wherein distinguishing between methylated and non methylated CpG dinucleotide sequences within the at least one target sequence comprises use of at least one nucleic acid molecule or peptide nucleic acid (PNA) molecule comprising, in each case a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under moderately stringent or stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:7, 8, 9, 10, 15, 16, 17 and 18, and complements thereof.

12. (Currently Amended) The method of claim 8, comprising:
extracting or otherwise isolating genomic DNA from a subject biological sample having genomic DNA;

treating the isolated genomic DNA, or a fragment thereof, with one or more reagents to convert cytosine bases that are unmethylated in the 5-position thereof to uracil or to another base that is detectably dissimilar to cytosine in terms of hybridization properties;

contacting the treated genomic DNA, or the treated fragment thereof, with an amplification enzyme and at least two primers comprising, in each case a contiguous sequence of at least 9 nucleotides that is complementary to, or hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:7, 8, 9, 10, 15, 16, 17 and 18, and complements thereof, wherein the treated genomic DNA or the fragment thereof is either amplified to produce at least one amplificate, or is not amplified; and

determining, based on a presence or absence of, or on a property of ~~said~~ the amplificate,

the methylation state of at least one CpG dinucleotide of SEQ ID NOS:2 and 3, or an average, or a value reflecting an average methylation state of a plurality of CpG dinucleotides of SEQ ID NOS:2 and 3, wherein at least one of detecting, or detecting and distinguishing between colon cell proliferative disorders is afforded.

13. (Previously Presented) The method of claim 12, wherein treating the genomic DNA, or the fragment thereof, comprises use of a reagent selected from the group consisting of bisulfite, hydrogen sulfite, and disulfite.

14. (Previously Presented) The method of claim 12, wherein contacting or amplifying comprises use of at least one method selected from the group consisting of: use of a heat-resistant DNA polymerase as the amplification enzyme; use of a polymerase lacking 5'-3' exonuclease activity; use of a polymerase chain reaction (PCR); and generation of a amplificate nucleic acid molecule carrying a detectable labels.

15. (Currently Amended) The method of claim 14, wherein ~~said~~ the nucleic acid molecule or peptide nucleic acid molecule is in each case modified at the 5'-end thereof to preclude degradation by an enzyme having 5'-3' exonuclease activity.

16. (Currently Amended) The method of claim 14, wherein ~~said~~ the nucleic acid molecule or peptide nucleic acid molecule is in each case lacking a 3' hydroxyl group.

17. (Original) The method of claim 16, wherein the amplification enzyme is a polymerase lacking 5'-3' exonuclease activity.

18. (Previously Presented) The method of claim 12, wherein determining comprises hybridization of at least one nucleic acid molecule or peptide nucleic acid molecule in each case comprising a contiguous sequence at least 9 nucleotides in length that is complementary to, or hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NOS:7, 8, 9, 10, 15, 16, 17 and 18, and complements thereof.

19. (Original) The method of claim 18, further comprising extending at least one such hybridized nucleic acid molecule by at least one nucleotide base.

20. (Previously Presented) The method of claim 12, wherein determining comprises sequencing of the amplificate.

21. (Previously Presented) The method of claim 12, wherein contacting or amplifying comprises use of methylation-specific primers.

22. (Withdrawn) A kit comprising a bisulfite reagent as well as at least one oligomer consisting essentially of at least one base sequence having a length of at least 10 contiguous nucleotides which hybridises to or is identical to a nucleic acid sequence selected from the group consisting of SEQ ID NOS:7, 8, 9, 10, 15, 16, 17 and 18.

23. (Canceled)

24. (Currently Amended) The method of claim 8, wherein distinguishing between methylated and non methylated CpG ~~dinucleotide~~ dinucleotide sequences within the target sequence comprises the use of methylation sensitive restriction enzymes.

25. (Canceled)